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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 403/14, A61K 31/41 — A1

(11) International Publication Number: **WO 95/21167**

(43) International Publication Date: 10 August 1995 (10.08.95)

(21) International Application Number: PCT/GB95/00135

(22) International Filing Date: 24 January 1995 (24.01.95)

(30) Priority Data:
9402011.2 2 February 1994 (02.02.94) GB

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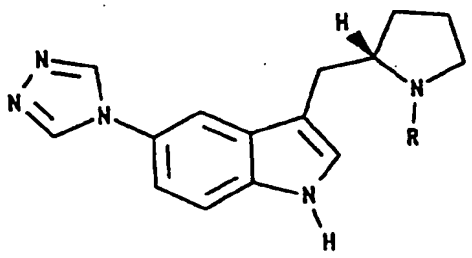
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.

(54) Title: TRIAZOLE DERIVATIVES

(57) Abstract

A compound of formula (I), or a salt or prodrug thereof wherein R represents hydrogen or C_{1-6} alkyl, selective agonist of 5-HT_1-like receptors and is therefore useful in the treatment of clinical conditions, in particular migraine and associated conditions, for which a selective agonist of these receptors is indicated.



(I)

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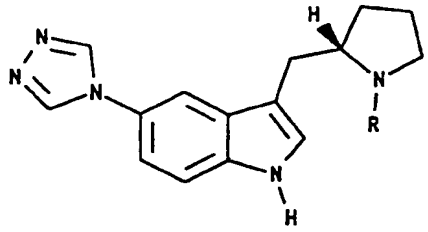
TRIAZOLE DERIVATIVES

The present invention relates to a discrete class of substituted triazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

WO-A-94/02477, published on 3rd February 1994, describes a class of substituted imidazole, triazole and tetrazole derivatives which are stated to be selective agonists of 5-HT_1-like receptors and hence to be of particular use in the treatment of migraine and associated conditions.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein R represents hydrogen or C_{1-6} alkyl.

As will be appreciated, the carbon atom at the 2-position of the pyrrolidine ring in the compounds of formula I above is in the (S) configuration. The compounds of formula I above, and salts and prodrugs thereof, are generically encompassed within the scope of WO-A-94/02477. There is, however, no specific disclosure therein of a compound corresponding to the compounds of formula I above, i.e. compounds wherein the carbon atom at the 2-position of the pyrrolidine ring is in the (S) configuration.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

As used herein, the expression "C_{1-6} alkyl" includes straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Such groups include

methyl and ethyl, and straight-chained or branched propyl, butyl, pentyl and hexyl. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Particular values for the group R include hydrogen and methyl.

Specific compounds within the scope of the present invention include:
(2S)-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine;
(2S)-N-methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine;
and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate,

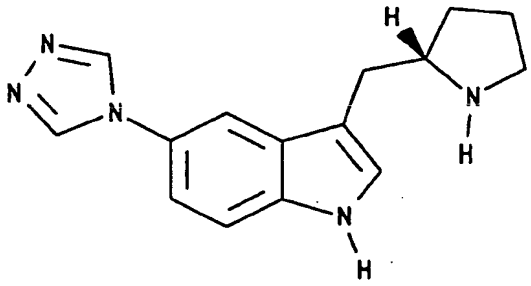
dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for

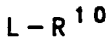
aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to this invention wherein R is other than hydrogen may be prepared by a process which comprises reacting the compound of formula IA with a compound of formula II:



(IA)



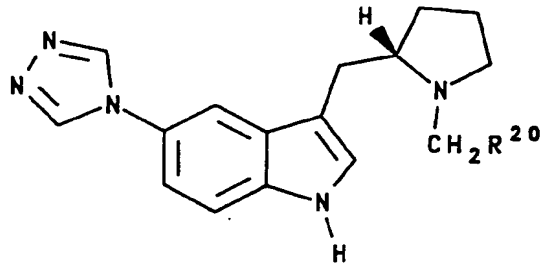
(II)

wherein R^{10} represents C_{1-6} alkyl, and L represents a suitable leaving group.

The leaving group L is suitably a halogen atom, e.g. bromine or iodine.

The reaction is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example in a dimethoxyethane and N,N-dimethylformamide solvent system in the presence of sodium carbonate, typically at the reflux temperature of the solvent.

In an alternative procedure, the compounds according to the invention represented by formula IB:

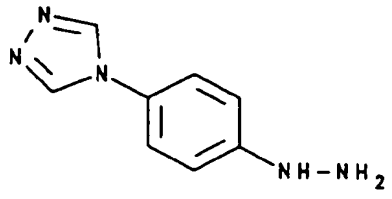


(IB)

wherein $-CH_2R^{20}$ corresponds to a group of formula R as defined above; may be prepared by a reductive amination process which comprises reacting a compound of formula IA as defined above with an aldehyde derivative of formula R^{20}-CHO in the presence of a reducing agent.

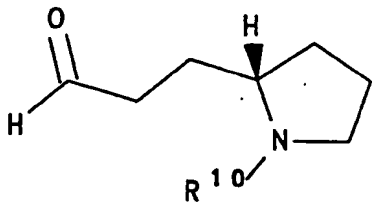
An appropriate reducing agent for use in this procedure is sodium cyanoborohydride, in which case the reaction is conveniently carried out in an alcoholic solvent such as methanol, typically in the presence of acetic acid.

In a further procedure, the compounds according to the invention wherein R is other than hydrogen, including the compounds of formula IB above, may be prepared by reacting the compound of formula III:



(III)

with a compound of formula IV or a carbonyl-protected form thereof:

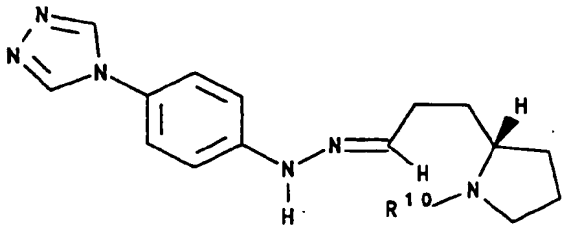


(IV)

wherein R^{10} is as defined above.

Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives.

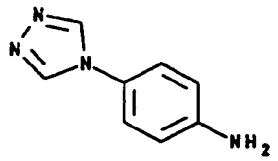
The reaction of compounds III and IV may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula V:



(V)

wherein R^{10} as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester.

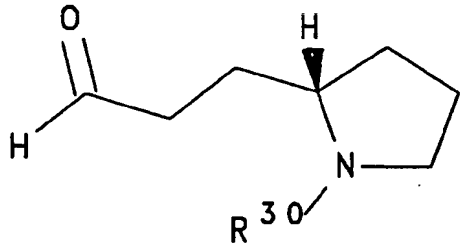
The hydrazine of formula III may be prepared from the corresponding aniline of formula VI:



(VI)

by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced <u>in situ</u> using, for example, tin(II) chloride/conc. HCl, sodium sulphite/conc. HCl, or sodium sulphite/conc. H_2SO_4.

The compounds of formula IA above may be prepared by reacting a compound of formula III as defined above with a compound of formula VII, or a carbonyl-protected form thereof:



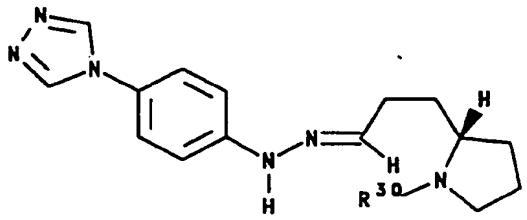
(VII)

wherein R^{30} represents hydrogen or an amino-protecting group; followed, where required, by removal of the amino-protecting group R^{30}.

As for compound IV, suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal and ketal derivatives.

The amino-protecting group R^{30}, where present, is suitably a lower alkoxycarbonyl moiety such as t-butoxycarbonyl (BOC), which can be conveniently removed as necessary by treatment with acid.

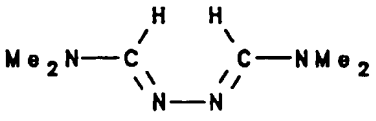
As with that between compounds III and IV, the reaction between compounds III and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:



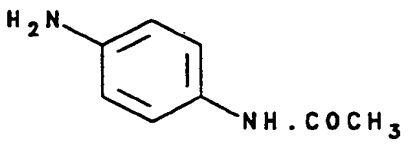
(VIII)

wherein R^{30} is as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The aniline derivative of formula VI may be prepared by reacting the hydrazine derivative of formula IX with the acetanilide of formula X:



(IX)



(X)

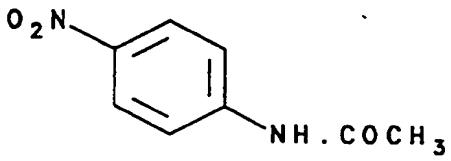
followed by removal of the N-acetyl protecting group.

The reaction between compounds IX and X is conveniently effected in refluxing toluene, advantageously in the presence of a catalytic quantity of p-toluenesulphonic acid. Subsequent removal of the N-acetyl protecting group is typically effected in hot aqueous 5N hydrochloric acid.

The hydrazine derivative of formula IX can be prepared from N,N'-diformylhydrazine by reaction with

thionyl chloride/N,N-dimethylformamide, as reported in J. Chem. Soc. (C), 1967, 1664, and subsequent treatment with sodium methoxide in methanol.

The acetanilide of formula X may be prepared by reduction of the corresponding nitro compound of formula XI:

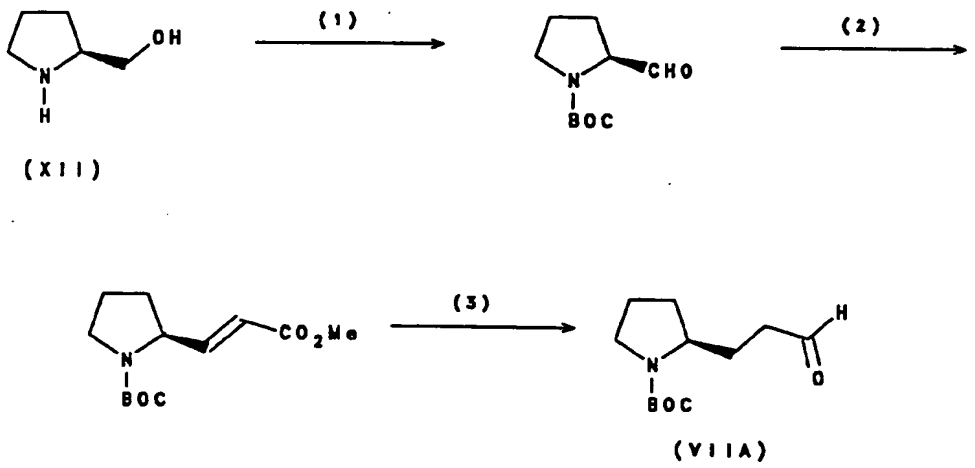


(XI)

typically by transfer hydrogenation using a hydrogenation catalyst in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

The nitro compound of formula XI is commercially available from the Aldrich Chemical Company Ltd., Gillingham, United Kingdom.

The preparation of a typical intermediate of formula VII above, protected on the ring nitrogen atom by a BOC group, is illustrated by the following reaction scheme:



The starting compound XII, L-prolinol, is commercially available from Aldrich Chemical Company Ltd., Gillingham, U.K. Step 1 of the reaction scheme involves protection of the pyrrolidine nitrogen as the N-BOC derivative, typically using BOC anhydride in dichloromethane; followed by Swern oxidation (oxalyl chloride/dimethyl sulphoxide/dichloromethane/-78°C, then triethylamine) of the terminal hydroxy group to an aldehyde moiety. Step 2 involves reaction with the Horner-Emmons reagent $MeO_2C.CH_2.PO(OEt)_2$ in the presence of sodium hydride, using THF as the solvent. In Step 3 the side-chain double bond is reduced, conveniently by catalytic hydrogenation over palladium-charcoal in aqueous methanol; and the methyl ester moiety is then partially reduced to an aldehyde functionality using DIBAL-H in THF at -78°C, to give the desired product of formula VIIA.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be

elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compound of formula IA, utilised as an intermediate in the above-described processes, is itself a compound in accordance with the present invention.

The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to 5-HT_1-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-^{3}H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC_{50}) is below 1 μM in each case.

The activity of test compounds as agonists of the 5-HT_1-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as $-\log_{10}EC_{50}$ (pEC_{50}) values, from plots of percentage 5-HT (1 μM) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC_{50} values in this assay of not less than 5.0 in each case.

EXAMPLE 1

(2S)-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl] methylpyrrolidine, 1.25 Oxalate

INTERMEDIATE 1

4'-(1,2,4-Triazol-4-yl)phenylhydrazine

Prepared from 4'-nitroacetanilide as described in WO 93/18029.

INTERMEDIATE 2

(2S)-N-*tert*-Butyloxycarbonyl-3-(pyrrolidin-2-yl)propanal

Prepared from L-prolinol as described herein on pages 10 to 11.

(2S)-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl] methylpyrrolidine. 1.25 Oxalate

A solution of Intermediate 1 (2.28g, 13.0mmol) and Intermediate 2 (2.50g, 11.0mmol) in 4% aqueous sulphuric acid (100ml) was stirred at room temperature for 0.3h and then heated at reflux for 36h. After cooling to room temperature, n-butanol was added and the aqueous basified with saturated aqueous potassium carbonate solution. The aqueous was separated and extracted further with n-butanol (x 3). The combined organics were evaporated *in vacuo* and the residue flash chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1), to give the title-*pyrrolidine* (1.01g, 34%). The oxalate salt was prepared, which crystallised out containing a small amount of ethanol; m.p. 118-120°C ($EtOH/Et_2O$); (Found: C, 55.52; H, 5.48; N, 18.17. $C_{15}H_{17}N_5 \cdot 1.25(C_2H_2O_4) \cdot 0.12 (C_2H_6O)$ requires C, 55.29; H, 5.29; N, 18.17%); ^1H NMR (360MHz, D_2O) δ 1.78 (1H, m, CH_2), 1.95-2.21 (3H, m, CH_2), 3.11-3.38 (4H, m, CH_2), 3.89 (1H, m, CH), 7.27 (1H, dd, J = 8.7 and 2.0Hz, Ar-H), 7.40 (1H, s, Ar-H), 7.59 (1H, d, J = 8.7Hz, Ar-H), 7.70 (1H, d, J = 1.9Hz), 8.80 (2H, s, Ar-H).

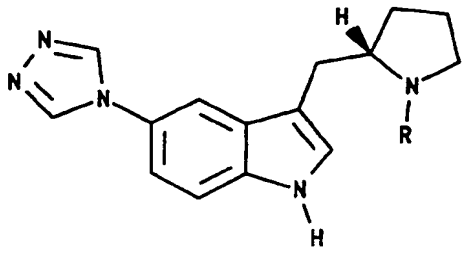
EXAMPLE 2

(2*S*)-N-Methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine. 1.4 Sulphate

To a cooled solution of the preceding NH-pyrrolidine (free base) (300mg, 1.12mmol), $NaCNBH_3$ (85mg, 1.35mmol) and acetic acid (0.16ml, 2.8mmol) in methanol (25ml) was added a solution of formaldehyde (110mg, 1.35mmol, 38% w/v) in methanol (15ml). The mixture was stirred at 0°C for 1.75h and then warmed to room temperature and stirred for 1.25h. Saturated K_2CO_3 solution was added and the solvent evaporated *in vacuo*. The aqueous was extracted with EtOAc (x 4), the combined extracts dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was flash chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give the title-*product* (258mg, 82%). The 1.4 sulphate salt was prepared which crystallised out containing a small amount of ethanol, m.p. 135°C; (Found: C, 45.98; H, 5.39; N, 16.32. $C_{16}H_{19}N_5$. 1.4(H_2SO_4). 0.12 (C_2H_6O) requires C, 45.98; H, 5.35; N, 16.51%); ^{1}H NMR (360MHz, D_2O) δ 1.84-2.06 (3H, m, CH_2), 2.24 (1H, m, CH_2), 2.85 (3H, s, CH_3), 3.11-3.19 (2H, m, CH_2), 3.38 (1H, dd, J = 14.7 and 5.9Hz, CH_2), 3.62-3.73 (2H, m, CH + 1 of CH_2), 7.38 (1H, dd, J = 8.7 and 2.0Hz, Ar-H), 7.48 (1H, s, Ar-H), 7.67 (1H, d, J = 8.7Hz,Ar-H), 7.84 (1H, d, J = 1.9Hz, Ar-H), 9.33 (2H, s, Ar-H).

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein R represents hydrogen or C_{1-6} alkyl.

2. A compound as claimed in claim 1 wherein R represents hydrogen or methyl.

3. (2S)-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine; and salts and prodrugs thereof.

4. (2S)-N-Methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine; and salts and prodrugs thereof.

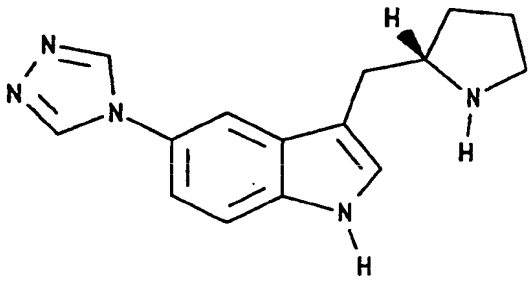
5. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

6. A compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for use in therapy.

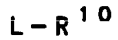
7. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated.

8. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reacting the compound of formula IA with a compound of formula II:



(IA)

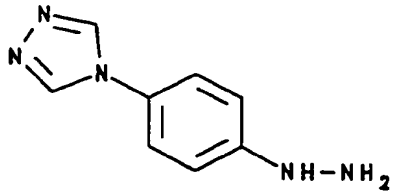


(II)

wherein R^{10} represents C_{1-6} alkyl, and L represents a suitable leaving group; or

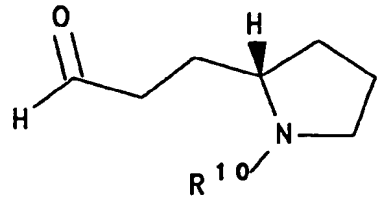
(B) reacting a compound of formula IA as defined above with an aldehyde derivative of formula R^{20}-CHO, wherein R^{20} represents hydrogen or C_{1-5} alkyl, in the presence of a reducing agent; or

(C) reacting the compound of formula III:



(III)

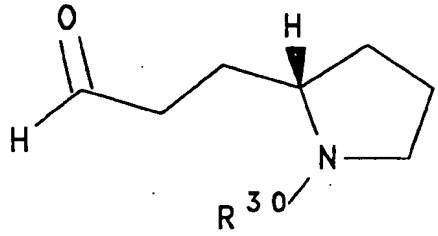
with a compound of formula IV or a carbonyl-protected form thereof:



(IV)

wherein R^{10} is as defined above; or

(D) reacting a compound of formula III as defined above with a compound of formula VII, or a carbonyl-protected form thereof:



(VII)

wherein R^{30} represents hydrogen or an amino-protecting group; followed, where required, by removal of the amino-protecting group R^{30}.

9. A method for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 95/00135

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 see claims ---	1-9
A	WO,A,93 21180 (PFIZER INC.) 28 October 1993 see claims ---	1-9
P,Y	EP,A,0 581 538 (MERCK SHARP & DOHME LTD.) 2 February 1994 see the whole document, especially page 4, formula IB ---	1-9
P,Y	WO,A,94 02477 (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see page 69; claims; examples 4,5 -----	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1995	22. 03. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB95/00135

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7 and 9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 95/00135

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0497512	05-08-92	AU-B-	644939	23-12-93
		AU-A-	1068092	06-08-92
		CN-A-	1064485	16-09-92
		JP-A-	5140151	08-06-93
		NZ-A-	241394	27-04-94
		US-A-	5298520	29-03-94
WO-A-9321180	28-10-93	AU-B-	3782193	18-11-93
		CA-A-	2132706	28-10-93
		EP-A-	0635015	25-01-95
		NO-A-	943803	07-10-94
EP-A-0581538	02-02-94	AU-B-	4215593	03-02-94
		WO-A-	9403446	17-02-94
		JP-A-	6184139	05-07-94
		CN-A-	1089262	13-07-94
WO-A-9402477	03-02-94	AU-B-	4578593	14-02-94
		CA-A-	2138649	03-02-94